16. A method of Claim 11 wherein said anti-TNFα antibody is a humanized antibody or antigen-binding fragment thereof.

17. A method of Claim 16 wherein said humanized antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.

18. A method of Claim 11 wherein said anti-TNFα antibody is a resurfaced antibody or antigen-binding fragment thereof.

19. A method of Claim 18 wherein said resurfaced antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.

REMARKS

Claims 1-6, 11-19 and 24-28 are under examination. Applicants have hereinabove canceled claims 24-28 without prejudice, and have amended claims 1 and 4. Support for the addition of the phrase "inflammatory disease" is found at, *inter alia*, page 7, lines 3-12. Applicants have also introduced certain format changes to the specification. A marked-up version of the amended paragraphs is annexed hereto as Exhibit A. Applicants maintain that these amendments raise no issue of new matter, and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 1-6 and 11-19 will be pending and under examination.

Pursuant to the requirements of 37 C.F.R. 1.121(b)(2), applicants annex hereto as Exhibit B claims 1 and 4 marked up to show the changes made herein relative to the previous version of those

claims.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the January 17, 2003 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides methods for treating or preventing an inflammatory disease in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts. In the preferred embodiment, the inflammatory disease is psoriatic arthritis.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-6 and 11-19 under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner asserted that claims 1-6 and 11-19 are indefinite, in (i) the recitation of the term "tumor necrosis factor-mediated disease", because the characteristics of said diseases are ill-defined and ambiguous, and (ii) the recitation of "TNF", since there are different members associated with TNF.

In response, applicants respectfully traverse. Without conceding the correctness of the Examiner's rejection, applicants point out

that the language objected to by the Examiner no longer appears in claims 1 and 4, as amended.

In view of the above remarks, applicants maintain that claims 1-6 and 11-19 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §102(e)

The Examiner rejected claims 1-6, 11, 13, 14, 19 and 24-28 under 35 U.S.C. §102(e) as allegedly anticipated by Mak (U.S. Patent No. 6,190,691). Applicants point out that claims 24-28 have been canceled. Accordingly, applicants understand the Examiner's rejection as directed to claims 1-6, 11, 13, 14 and 19.

In response to the Examiner's rejection, applicants respectfully traverse.

Briefly, claims 1-6, 11, 13, 14 and 19 provide methods for treating or preventing an inflammatory disease in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts. In preferred embodiments, the inflammatory disease is psoriatic arthritis and the TNFα antagonist is an anti-TNFα antibody or antigen-binding fragment thereof.

To anticipate the methods of claims 1-6, 11, 13, 14 and 19, Mak would have to teach each and every element thereof. It fails to do this.

Mak teaches methods of suppressing TNF production and treating inflammation, and pharmacological agents for use therein.

Mak states that the pharmacological agents which are useful in this aspect of the invention are from a *broad* range of agents known in the literature for other diverse activities (column 30, lines 2-4). Indeed, from column 29, line 60 through column 43, line 2, Mak organizes the agents into several groups, each group containing representative examples, the combined total of these examples numbering in the *hundreds*.

Regardless of whether the agents used in the claimed invention are both disclosed in Mak, there is no specific disclosure of the *claimed combination* of methotrexate and a TNFα antagonist, or of methotrexate and anti-TNFα antibody, to treat or prevent an inflammatory disease. Thus, the combination of agents used in the claimed invention represents only one of an astronomical number of permutations of the pharmacological agents disclosed by Mak. Applicants stress that teaching a list of agents from which a particular subset thereof is claimed does not constitute disclosing the claimed subset. Therefore, Mak fails to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 1-6, 11, 13, 14 and 19 satisfy the requirements of 35 U.S.C. §102(e).

Rejection Under 35 U.S.C. §103

The Examiner rejected claims 1-6, 11-14, 16-19 and 24-28 under 35 U.S.C. §103 as allegedly unpatentable over Mak and/or Adair, et al.

(U.S. Patent No. 5,994,510) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437) and Aggarwal, et al. (U.S. Patent No. 5,672,347). Applicants point out that claims 24-28 have been canceled. Accordingly, applicants understand the Examiner's rejection as directed to claims 1-6, 11-14 and 16-19.

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Again, claims 1-6, 11-14 and 16-19 provide methods for treating or preventing an inflammatory disease in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts. In preferred embodiments, the inflammatory disease is psoriatic arthritis and the TNFα antagonist is an anti-TNFα antibody or antigen-binding fragment thereof.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First the cited references, when combined, must teach or suggest every element of the claims. Second, one of ordinary skill must have been motivated to combine the teachings of the cited references at the time of the invention. Third, there must be a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, Mak and/or Adair, et al., when combined with the Merck

Manual of Diagnosis and Therapy (Merck) and Aggarwal, et al., must create a motive to combine and a reasonable expectation of success.

Mak is discussed above. Again, this reference does not teach or suggest a combination of methotrexate and a TNFα antagonist, or of methotrexate and anti-TNFα antibody, to treat or prevent an inflammatory disease.

Adair, et al. teach the use of recombinant anti-TNF antibody, but not methotrexate. Merck teaches the use of methotrexate, but not a TNF antagonist, in the treatment of inflammatory disease. In essence, the Examiner has combined references teaching the treatment of a disorder, wherein each reference teaches the use of one, but not the other, of the agents used in the claimed method. However, the Examiner has not properly shown a motive to combine these references, or a reasonable expectation of success.

Aggarwal, et al. fail to cure this deficiency. Aggarwal, et al. teach generally that combinations of certain agents can be used in lesser dosages than when used alone. They do not teach or suggest the combination of methotrexate and anti-TNFα antibody (or TNFα antagonist) in the treatment or prevention of inflammatory diseases.

In light of these teachings and their shortcomings, the Examiner has failed to show how the cited references, when combined, would have created a motive to combine or a reasonable expectation of success.

In support of their position, applicants draw the Examiner's attention to the unexpected results of treating an inflammatory disorder with a combination of methotrexate and a TNF antagonist. These results are exemplified by the data set forth in Figures 1A, 2A, 3A, 4A, 5A and Table 4 of the specification. Applicants also draw the Examiner's attention to the unexpected result that combination therapy with methotrexate and a TNF antagonist produced high clinical response rates for significantly longer durations in comparison with that obtained with treatment with each therapeutic modality separately (see, e.g., page 3, lines 18-24, Examples 1-3; particularly, page 35, lines 5-8, page 37, lines 1-3, pages 36-37 (Table 3), pages 38-39 (Table 4), page 46, line 24 through page 47, line 8 of Example 1; page 48, line 20 through page 50, line 8 of Example 2; and page 51, lines 8-32 of Example 3). The magnitude of these results, particularly in the treatment of inflammatory disease, could not have been predicted from the cited references.

As further evidence in support of the surprising and unexpected nature of applicants' invention, applicants cite Verhoeven, et al. (attached hereto as Exhibit C). Figure 1 of Verhoeven, et al. shows a three-dimensional survey of the efficacy of combination therapy in treating inflammatory disease, i.e., rheumatoid arthritis, relative to the efficacy of the individual drugs in the combination. As Figure 1 clearly shows, even when drugs which are successful in treating rheumatoid arthritis alone are combined, many of these combinations do not improve treatment at all. In other words, Verhoeven, et al. only underscore the fact that superior effects of a particular combination therapy in the treatment of inflammatory disease are not predictable absent experimentation.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1-6, 11-14 and 16-19 over Mak and/or Adair, et al., when combined with the Merck Manual of Diagnosis and Therapy (Merck) and Aggarwal, et al.

In view of the above remarks, applicants maintain that claims 1-6, 11-14 and 16-19 satisfy the requirements of 35 U.S.C. §103.

The Examiner also rejected claims 14 and 15 under 35 U.S.C. §103 as allegedly unpatentable over Mak and/or Adair, et al. (U.S. Patent No. 5,994,510) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437) and Aggarwal, et al. (U.S. Patent No. 5,672,347) as applied to claims 1-6, 11-14, 16-19 and 24-28 above and further in view of Le, et al. (U.S. Patent No. 5,919,452).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Claims 14 and 15 provide methods for treating or preventing an inflammatory disease in an individual in need thereof comprising co-administering methotrexate and the chimeric anti-TNFα antibody cA2, or a competitive inhibitor thereof, to said individual, in therapeutically effective amounts.

Mak, Adair, et al., Merck and Aggarwal, et al. are discussed above.

Le, et al. teach the use of chimeric anti-TNFα antibodies, including cA2, to treat TNF-related pathologies. Le, et al. fail

to cure the deficiencies of the above-cited references as discussed above, and thus, the combination of this reference with the other cited references does not create a motive to combine and a reasonable expectation of success.

In view of the above remarks, applicants maintain that claims 14 and 15 satisfy the requirements of 35 U.S.C. §103.

Summary

In view of the foregoing remarks, applicants respectfully request that the above grounds of rejection be reconsidered and withdrawn and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the $410.00 fee for a two-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
Tel. No. (212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

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6/17/03

Alan J. Morrison Date
Reg. No. 37,399

Page 1, lines 8-16:

This application is a continuation of U.S. Application No. 08/690,775, filed August 1, 1996, now U.S. Patent No. 6,270,766, which is a continuation-in-part of U.S. Application No. 08/607,419, filed February 28, 1996, now abandoned, which is a continuation-in-part of International Application No. PCT/GB94/00462, filed March 10, 1994, which is a continuation-in-part of U.S. Application No. 08/403,785, now U.S. Patent No. 5,741,488, which is the U.S. National Phase of International Application No. PCT/GB93/02070, filed October 6, 1993, which is a continuation-in-part of U.S. Application No. 07/958,248, filed October 8, 1992, now abandoned, the teachings of all of which are entirely incorporated herein by reference.

Marked-Up Version of Amended Claim

1. (Amended) A method for treating or preventing [a tumor necrosis factor-mediated] an inflammatory disease in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts.

4. (Amended) A method of Claim 1 wherein the [tumor necrosis factor-mediated] inflammatory disease is [selected from the group consisting of: autoimmune disease, acute or chronic immune disease, inflammatory disease and neurodegenerative disease] psoriatic arthritis.